



[Home](#) » [News & Events](#) » [NIDA Notes](#) » [Basic Science](#) » **A Gene Links Impulsivity and Drug Use Vulnerability**

A Gene Links Impulsivity and Drug Use Vulnerability

June 14, 2018

By William Ross Perlman, Ph.D., CMPP, NIDA Notes Contributing Writer

This research:

- Identified a gene variant that promotes impulsive behavior and enhanced responses to heroin in rats.
- Linked the corresponding human gene variant to increased risk for impulsivity and drug use.

People who are highly impulsive and those diagnosed with ADHD are at increased risk for substance use disorders (SUD). Recent research implicates a variant of the gene for a protein called cAMP-response element modulator (CREM) in these associations. Drs. [Michael L. Miller](#) and [Yasmin L. Hurd](#) from the Icahn School of Medicine at Mount Sinai in New York, with colleagues from several other institutions, showed that the gene variant promotes impulsive and hyperactive behavior in both animals and humans, and can contribute to a person's risk for developing SUD.

Of Rats...

The Icahn researchers began their investigations with a strain of rats that exhibit impulsive behaviors resembling human attention-deficit/hyperactivity disorder (ADHD). Initial experiments confirmed that, compared with a strain (Western Kyoto) of rats that are not known for impulsivity, these "spontaneously hypertensive" (SH) rats:

- Were more impatient to receive rewards, fidgeted more while waiting to receive rewards, ran around more, and were more attracted to novel experiences.

- Self-administered more heroin and, when it was made unavailable, gave up seeking it less readily.
- Had enhanced elevation of dopamine levels in response to heroin.

The researchers screened the rats' DNA for genetic differences that might contribute to these behavioral differences. The results revealed that the two strains carried different variants of the gene for CREM. As a result, the SH rats had lower concentrations of CREM in the core of the nucleus accumbens—a key brain region governing reward and movement.

...And People

The researchers used genetic and behavioral evidence from previous studies conducted by other researchers to demonstrate that the corresponding variant in the human *CREM* gene similarly predisposes people to impulsivity. This variant occupies approximately the same position on the human gene that the rodent variant occupies on the rodent gene. At this site, known as rs12765063, the *CREM* gene exists in two versions—called A and G—and the A variant dials down CREM production. In one study, preschool children with the A variant were found to be more distractible and to engage in more dangerous activities than peers with only the G variant (Figure 1). In another, among adolescents with ADHD, those who carried the A variant reported more symptomatic hyperactivity than those who did not.

The researchers further found that by promoting impulsivity, the variant raises the risk of drug use. Thus, in two studies of adolescents, neither the A variant alone nor ADHD alone increased the risk for drug use, but the two together did. The first analysis looked at adolescents with ADHD, and found higher rates of drug use among those with the A variant than among those with only the G variant. The second analysis looked at adolescents who had the A variant of rs12765063 and histories of childhood ADHD. It found that those whose childhood ADHD still persisted reported more use of alcohol, tobacco, marijuana, and prescription stimulants than those who had outgrown their ADHD (Figure 2). Moreover, those who no longer had ADHD reported no more drug use than a comparison group who did not carry the A variant.

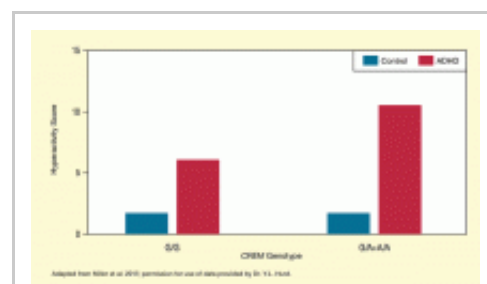


Figure 1. A *CREM* Gene Variant Increases Hyperactivity Hyperactivity scores were higher in ADHD subjects than in control subjects. In addition, ADHD subjects who carried at least one copy of the less highly expressed A variant (i.e., with the G/A or A/A *CREM* genotype) reported significantly higher hyperactivity than did those carrying only the more highly expressed G variant (i.e., with the G/G genotype). Genotype had no effect on hyperactivity in non-ADHD control subjects. [Text Description of Graphic](#)

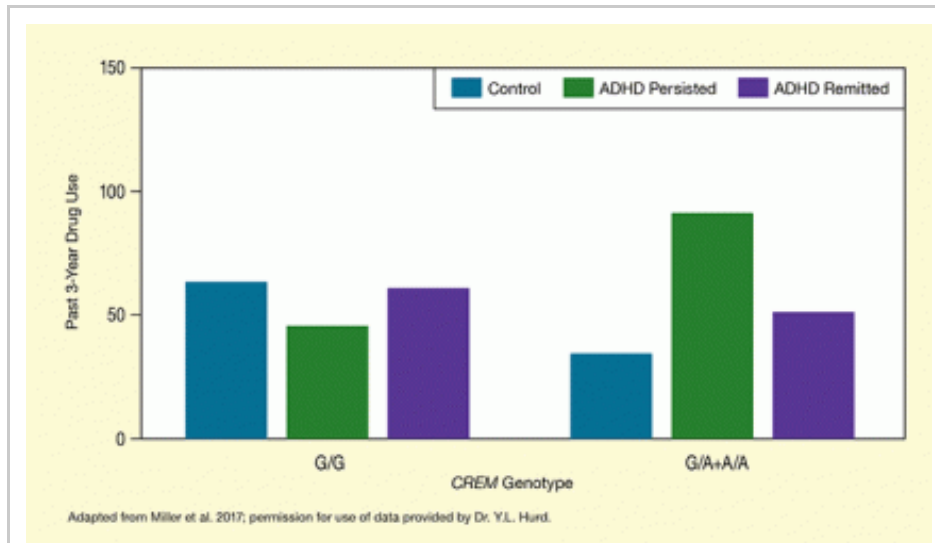


Figure 2. The A Variant of the *CREM* Gene Is Associated With Increased Drug Use in People With Persistent ADHD

Among a cohort whose childhood ADHD persisted through adolescence, those with the *CREM* A variant reported more drug use than those with only the G variant. Genotype was not linked to risk for drug use in people without ADHD (i.e., those who never had ADHD or those with remitted ADHD).

[Text Description of Graphic](#)

A Key to Prevention and Treatment?

Dr. Hurd suggests that *CREM* may be a key link between impulsivity and vulnerability to addiction. Understanding these relationships may help identify new ways of treating or preventing SUD. The protein is known to regulate multiple gene networks and their biological functions, and to influence the growth of structures that neurons use to communicate with each other.

Dr. Hurd says, "These results highlight that *CREM* is a mediating factor between impulsivity and substance abuse vulnerability. It brings attention to *CREM* in the nucleus accumbens as a regulator of impulsive action and structural plasticity."

The study was supported by NIH grants DA015446, DA030359, DA006470, DA038954, DA031559, and DA007135.

Source:

Miller, M.L., Ren, Y., Szutorisz, H., et al. [Ventral striatal regulation of *CREM* mediates impulsive](#)

[action and drug addiction vulnerability](#). *Mol Psychiatry* 23(5):1328-1335, 2018. Published online 2017 Apr 25. doi: [10.1038/mp.2017.80](https://doi.org/10.1038/mp.2017.80)

Receive articles like this in your inbox monthly!

This page was last updated June 2018

NIH...Turning Discovery Into Health®

